Discussion of the Amendment

Claims 5 and 6, and claim 8 to 12 have been cancelled as being drawn to non-elected subject matter. Applicants reserve the right to pursue the subject matter of these cancelled claims in pending or subsequently filed divisional, continuation or continuation-in-part applications.

Claim 1 has been amended to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

This amendment to the claims adds no new matter.

Discussion of the Rejections Under 35 U.S.C. § 102

Claims 1 to 4, and 7 stand rejected under 35 U.S.C. § 102 (b) as, the Examiner alleges, being anticipated by Tang et al., U.S. Patent No. 5,792,783 (hereinafter, "Tang 1"). (Office Action at 3). Applicants respectfully traverse this rejection.

It is well-settled that a species is not necessarily anticipated by a prior disclosed genus encompassing the species. (See, for example, MPEP 2131.02; *In re Petering and Fall*, 133 U.S.P.Q. 275 (CCPA 1962); *Ex parte A*, 17 U.S.P.Q.2d 1716 (BPAI 1990). Among the factors to be considered in the analysis of the genus/species situation are: (1) the size of the disclosed genus; (2) whether there is a specific disclosure of the species in the reference disclosing the species; and (3) the amount of guidance, or lack thereof, given in the reference for selecting the species.

The number of compounds disclosed by each of the genera of Tang 1 is enormous. However, nowhere in Tang 1 are the compounds as defined by the claims of the present invention specifically disclosed. Further, no guidance is found in Tang 1 to lead a person skilled in the art to specifically pursue the compounds of the present application. This is true for all compounds of the present invention.

In particular, for the compound of Applicants' elected species, 1,3-dihydro-3-(imidazol-4-ylmethylene)-5-pyrid-3-yl)-2H-indolin-2-one, and for the compound 1,3-dihydro-3-(pyrrol-2-ylmethylene)-5-pyrid-3-yl)-2H-indolin-2-one. It is to these compounds that the Examiner has apparently limited the search (Office Action at 2). None of the compounds exemplified or specifically disclosed by Tang 1 contain an imidazolylmethylene moiety at the 3-position (or any other position for that matter) of the indolinone ring. Further, the only moieties specifically disclosed by Tang 1 at the 5-position are chloro, nitro and methoxy. None of the compounds exemplified or specifically disclosed by Tang 1 contain any aromatic moiety at the 5-position, let alone the pyridyl moiety as required by the two compounds of the Examiner's search.

Further, there is no disclosure in Tang 1, nor any suggestion of using the compounds disclosed therein as inhibitors of CDK-1.

Because the genera of Tang 1 encompass an enormous number of compounds; because there is no specific disclosure of any of the compounds of the present invention; because there is no guidance in Tang 1 as to the desirability of the particular moieties and placement thereof on the indolinone ring as required by the compounds of the present invention; and because the compounds of the present invention have a utility undisclosed by Tang 1, Tang 1 can not be an anticipating reference under 35 U.S.C. § 102(b).

Claims 1 to 4, and 7 stand rejected under 35 U.S.C. § 102(a) as, the Examiner alleges, being anticipated by Tang et al., U.S. Patent No. 6,316,429 (hereinafter, "Tang 2"). (Office Action at 4). Applicants respectfully traverse this rejection.

The discussion above applies also to Tang 2. The generic disclosure of Tang 2 is absolutely enormous. Meanwhile, Table 1 of Tang 2 lists 133 starting indolinones, and 112 starting aldehydes, giving rise to almost 15,000 compounds which may be thought of as specifically disclosed. In spite of this, there is no specific disclosure of any of the compounds as defined by the claims of the present invention.

Applicants acknowledge that pyrroles, thiophenes, and furans are listed in Table 2 of Tang 2 and, as such, form substituents analogous to the "Ar" portion of Applicants' Formula 1. However, these aromatic substituents are invariably substituted with one or more carboxyalkyl substituents, or esters or amides thereof. These substituents could certainly have an effect on the properties of the molecules. These substituents are simply not present in any of the compounds of the present application, and there is no specific indication in Tang 2 that compounds so unsubstitued would be useful as kinase inhibitors.

Further, and again with respect to the Examiner's searched compounds, there is no specific disclosure of any imidazole at the 3-position of the indolinone ring, as required by Applicants' elected species, and there is no disclosure of any directly attached aromatic ring at the 5-position, let alone any disclosure of pyridyl, as required by the elected species, and the species to which the Examiner extended the search.

With respect to Tang 2, the Examiner indicates that, "A CDK2 inhibition assay was also completed." (Office Action at 4). Applicants' respectfully disagree.

Looking at column 87, and following, of Tang 2, Applicants acknowledge that an assay for CDK2 is described. However, nowhere in Tang 2 is any CDK2 inhibition data given for any of the almost 15,000 compounds specifically disclosed. Therefore, there can certainly be no guidance or suggestion to direct a person skilled in the art to pursue the undisclosed compounds of the present application for CDK2 inhibition. Finally, of course, CDK-1 and CDK2 are, indeed, different enzymes, and a compound that inhibits one may or may not inhibit the other.

As with Tang 1, there is simply nothing to guide or motivate a person skilled in the art to pursue the specific compounds encompassed by the claims of the present application. Tang 2 may not be used as an anticipating reference in this case.

Accordingly, in view of the present amendment, and the above remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully requested.

Discussion of the Rejections Under 35 U.S.C. § 103

Claims 1 to 4, and 7 stand rejected under 35 U.S.C. § 103(a) as, the Examiner alleges, being unpatentable over Tang et al., U.S. Patent No. 6,133,305 (hereinafter, "Tang 3"), in view of Tang 1. Applicants respectfully traverse this rejection.

It is well-settled that a species or sub-genus is not necessarily rendered obvious by a prior disclosed genus. (See, for example, *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994); *In re Jones*, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); and MPEP 2144.08). Among the factors to be considered are the size of the disclosed genus, the express teachings of the reference disclosing the genus, the teachings of structural similarities, the teaching of similar properties or uses, and the predictability of the technology (MPEP 2144.08).

As in the cases of Tang 1 and Tang 2, the generic disclosure of Tang 3 is massive. Further, looking at Tables 1 and 2 of Tang 3, combining the indolinones and aldehydes of Tables 1 and 2, respectively, gives rise to almost 2,000 compounds that can be thought of as specifically disclosed. None of the compounds encompassed by the claims of the present application are specifically disclosed. In particular, and as the Examiner acknowledges, Tang 3 does not disclose acetylamino or heteroaryl at the 5-position of the indolinone ring.

The Examiner suggests that, "At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute [the alkyl substituent at the 5-position] of [Tang 3] with a pyridyl substituent of [Tang 1] to explore its use as a modulator of the activity of protein kinases such as the serine-threonine kinases, CDK's." (Office Action at 5).

Applicants respectfully disagree, and maintain this is not the case, and that there is no "teaching of structural similarities" or motivation.

Applicants acknowledge that Tang 3 discloses an indolinone substituted at the 3-position by a pyrrol-2-ylmethylidenyl or imidazol-4-ylmethylidenyl (see examples 10717/H04, 10717/H09, 10724/H09 and 10725/H11 in Table 3 of Tang 3). However, these examples are

invariably substituted with halogen atoms at positions 5 and 7 of the indolinone ring. Nothing in Tang 3 would suggest to, or motivate a person skilled in the art to key on or pursue these particular examples out of the hundreds of others. There would be even less motivation to combine these four examples with the disclosure of Tang 1 to arrive at the compounds of the present invention, absent the disclosure of the present application.

The Examiner appears to be using the disclosure of the present application and hindsight to suggest motivation to combine Tang 1 and Tang 3. Such use of hindsight in an obviousness analysis is impermissible. (See, for example, *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988), and MPEP 2143.01).

It is well settled that obviousness to try, without a reasonable expectation of success is not the proper standard under 35 U.S.C. § 103. (See, for example, MPEP 2143.02; *In re Eli Lilly & Co.*, 14 U.S.P.Z.2d 1741, 1743 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988)). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." (*In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988)).

The compounds of the present application are inhibitors of the Cdc2/cyclin B (CDK-1) enzymatic complex, which is responsible for initiating phase M of the cell cycle. Modulation of the activity of CDK-1 is a key mechanism for halting cell proliferation. (See, for example, the present specification at page 2).

Tang 1 relates to compounds that modulate or inhibit tyrosine kinase signal transduction. Tang 1 does not describe the use of the compounds disclosed therein as specific inhibitors of CDK-1, in particular in order to stop cell proliferation at phase G2/M. Similarly, Tang 3 does not specifically disclose the use of the compounds disclosed therein to inhibit CDK-1.

Thus, even if combining Tang 1 and Tang 3 were to somehow render it obvious to try compounds of the present invention as CDK-1 inhibitor (which, as discussed above, it does not)

there could certainly be no expectation of success derived from the disclosures of Tang 1 and Tang 3.

Accordingly, in view of the present amendment and above remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

In view of the present amendment and the above remarks, Applicants submit that the invention as defined by the claims of the present application is novel and non-obvious over the prior art, and complies with the provisions of 35 U.S.C. § 112. Therefore, allowance and passage to issue of Claims 1 to 4, and 7 are respectfully requested.

Respectfully submitted,

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